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(54) Title: (PHOSPHO)LIPIDS FOR COMBATTING HEPATITIS B VIRUS INFECTION

(57) Abstract

A method of treating hepatitis B virus is disclosed. The method comprises administering to a subject in need of such treatment a hepatitis B combatting amount of alkyl ether phospholipids and alkyl ether phospholipid derivatives.

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METHOD OF COMBATTING HEPATITIS B VIRUS INFECTION

Field of the Invention

This invention relates generally to the treatment of hepatitis B virus, and more specifically to the treatment of hepatitis B virus with alkyl ether phospholipids and alkyl ether phospholipid derivatives.

Background of the Invention

The human hepatitis B virus (HBV) is one of a family of hepadnaviruses that cause acute and chronic liver disease, including liver cancer. The virus is found in the body fluids of infected persons. Recognized risk factors for infection include blood transfusion, sexual contact, hemodialysis, shared intravenous needles, acupuncture, tissue transplantation and the like.

The virus makes three antigenic proteins during multiplication in liver cells: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBcAg). These three virus antigenic proteins are important as markers for determining virus infection, as antibodies against the virus infection are made in response to these virus proteins in the blood.

Currently, there are no specific antiviral agents to treat acute or chronic persistent hepatitis. An HBV vaccine is available to prevent infection, and hyperimmune gamma globulin is available for temporary

prophylaxis against developing HBV infection in persons at risk. Clearly specific antiviral agents are needed for treatment and control of HBV infections in humans.

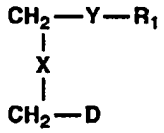
Alkyl ether phospholipids and derivatives are known potent biologic agents that effectively inhibit tumor cell growth and HIV-1 multiplication. *See*, Marx et al., J. Med. Chem. **31**:858-863 (1988), and Kucera et al., AIDS Res. Human Retroviruses **6**:491-501 (1990). The major sites of action of these agents involves the plasma membrane of tumor cells, HIV-1 infected cells and protein kinase C.

Based on the foregoing, it is an object of the present invention to provide a new treatment method for combatting the effects of HBV and for inhibiting HBV-DNA and virion production.

It is a second object of the present invention to provide compositions for carrying out the same.

Summary of the Invention

These and other objects are satisfied by the present invention, which as a first aspect provides a method of combating HBV in a subject in need of such treatment. The method comprises administering to the subject in an amount effective to inhibit HBV-DNA replication and virion production a compound of Formula I:



(I)

wherein

Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl;

X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

and D is selected from the group consisting of moieties of Formula V or Formula VI;

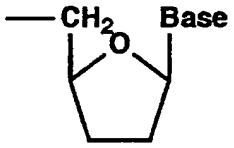
wherein Formula V is

$$-(PO_4)^-\text{-}E \qquad (V)$$

wherein E is selected from the group consisting of:

$-F-N^+(R_2)(R_3)(R_4)$, wherein F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl; and R_2, R_3, and R_4 are independently selected from the group consisting of H and C1-C3 alkyl; and

a nucleic acid base conjugate of the Formula VII



(VII)

wherein the base is selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine; A is H, F, or N_3; and B is H or F, or A and B together form a covalent bond;

and wherein Formula VI is (VI)

$$-N^+(R_5)(R_6)\text{-}F\text{-}W\ Z^-$$

wherein R_5 and R_6 are independently selected from the group consisting of H and C1-C3 alkyl;

F is as defined above;

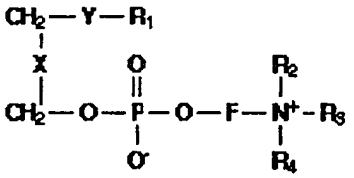
W is -OH, or -SH; and

Z^- is an anion;

or a pharmaceutical salt thereof.

A second aspect of the present invention is a method of inhibiting the production of a hepatitis B virus antigen selected from the group consisting of core antigen and e antigen. The method comprises administering to a subject an effective antigen-production limiting amount of a compound of Formula I.

A third aspect of the present invention is a method of combating HBV infection in a subject in need of such treatment. The method comprises administering to the subject in an amount effective to inhibit HBV-DNA replication and virion production a compound of Formula II:



(II)

wherein

Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl;

X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl; and

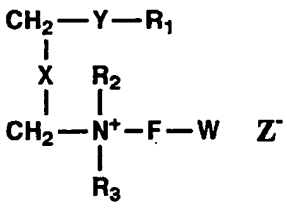
R_2, R_3, and R_4 are independently selected from the group consisting of H and C1-C3 alkyl;

or a pharmaceutical salt thereof.

A fourth aspect of the present invention is a method of inhibiting the production of a hepatitis B virus antigen selected from the group consisting of core

antigen and e antigen. The method comprises administering to a subject an effective antigen-production limiting amount of a compound of Formula II.

A fifth aspect of the present invention is a method of combatting hepatitis B virus infection in a subject in need of such treatment comprising administering to the subject a compound of Formula III



(III)

wherein

Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl;

X is a covalent bond or methylene optionally substituted 1 or 2 times with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl;

R_2 and R_3 are independently selected from the group consisting of H and C1-C3 alkyl;

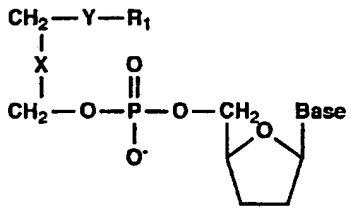
W is -OH, or -SH; and

Z^- is an anion.

The compound is administered in an amount effective to combat the hepatitis B virus infection.

A sixth aspect of the present invention is a method of inhibiting the production of a hepatitis B virus antigen selected from the group consisting of core antigen and e antigen. The method comprises administering to a subject an effective antigen-production limiting amount of a compound of Formula III.

A seventh aspect of the present invention is a method of combatting hepatitis B virus infection in a subject in need of such treatment comprising administering to the subject a compound of Formula IV.



(IV)

wherein

Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl,

X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

The base is selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine;

A is H, fluorine, or N_3; and B is H or flourine, or A and B together form a covalent bond.

An eighth aspect of the present invention is a method of inhibiting the production of a hepatitis B virus antigen selected from the group consisting of core antigen and e antigen. The method comprises administering to a subject an effective antigen-production limiting amount of a compound of Formula IV.

A ninth aspect of the present invention is the use of an alkyl ether phospholipid or alkyl ether phospholipid derivative of formulas I, II, III, or IV given above for the preparation of a medicament combatting HBV infection and inhibiting HBV virion production.

Detailed Description of the Invention

As used herein, the term "alkyl" is intended to refer to an unbranched or branched alkyl group comprising carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, hexyl, and octyl. This definition also applies to an alkyl moiety in the alkoxy group. Examples of alkoxy groups are methoxy, ethoxy, propoxy, sec-butoxy, and isohexoxy. Similarly, the term "alkenyl" means an unbranched or branched alkenyl group comprising carbon atoms and having at least one double bond, such as ethenyl, propenyl, isopropenyl, n-butenyl, tert-butenyl, hexenyl, and octenyl. The term "alkynyl" means an unbranched or branched alkynyl group comprising carbon atoms and having at least one triple bond. The term "pharmaceutical salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart undesired toxicological effects thereto. Examples of such salts are (a) salts formed with cations such as sodium, potassium, NH_4^+, magnesium, calcium polyamines, such as spermine, and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The term "amphipathic" refers to a compound having both a polar hydrophilic end and a non-polar hydrophobic end. The term "amphoteric" refers to a compound that has both a negative and positive charge within the same compound.

The present invention is directed to the treatment of HBV infection. It has been discovered that the compounds of Formulas I, II, III and IV above can be used to treat HBV and virion production in subjects in need of such treatment, as HBV is combatted by administration of alkyl ether phospholipids or derivatives thereof to such subjects. While the inventors do not wish to be bound by any mechanism that explains how these compounds combat HBV infection, it has also been observed that production of HBV core and e antigens is inhibited by treatment with these compounds. It is believed that the site of action most likely involves inhibition of HBV-DNA and post-transcriptional protein synthesis and replication at cell membranes.

A first aspect of the invention is a method of inhibiting HBV-DNA and HBV antigen virion production using a compound of Formula I, wherein R_1, Y, X, and D R_4 are defined as stated above, or a pharmaceutical salt thereof. The compounds of Formula I are amphipathic moieties having a short alkyl backbone (represented by C-X-C in Formula I), a hydrophobic end represented by R_1 linked to one end of the alkyl backbone by the functional group Y, and a hydrophilic end D linked to the other end of the short alkyl chain. D is generally amphoteric and is preferably a phospho-ammonium or -nucleic acid-base complex (Formula V) or an alkyl ammonium-anion complex (Formula VI).

Formulas II, III, and IV represent preferred embodiments of the compounds of Formula I. The individual components of each are described in detail below.

In Formula II, as described above, R_1 is a lipophilic moiety; the lipophilicity of R_1 allows the compounds of Formula II to bind with the cell membrane of a cell infected with the HBV retrovirus to provide an anchor thereto. R_1 can be an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or

alkynyl. Preferably, R_1 is an unbranched saturated or unsaturated C12-C20 alkyl group, and more preferably, R_1 is a lipophilic moiety comprising an unbranched saturated or unsaturated C14-C18 alkyl group.

In compounds of Formula II, Y is a functional group that links the lipophilic moiety R_1 and the short alkyl backbone of the compound. Y should be a functional group, such as S, O, NH, NCH_3, NHCO, or NCH_3CO, that is able to withstand the hydrolytic activity of cellular lipases. Preferably, Y is S or NHCO.

The alkyl backbone includes a constituent X which can be a covalent bond between the carbon atoms at either end of the backbone or a methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio. Preferably, X is a covalent bond or a methylene substituted with a hydroxyl or C1-C4 alkoxy; more preferably, X is methylene substituted with hydroxyl or methoxy.

The polar hydrophilic end of the amphipathic compounds of Formula II comprises an amphoteric ammonium phosphoalkyl group in which the phosphate moiety carries the negative charge and the ammonium moiety carries the positive charge. In the ammonium phosphoalkyl group, n is a number between 1 and 4 and R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen and C1-C3 alkyl. It is preferred that F be unsubstituted ethylene. It is also preferred that R_2, R_3, and R_4 are each methyl. It is particularly preferred that F is unsubstituted ethylene and R_2, R_3, and R_4 are each methyl.

Exemplary compounds of Formula II include rac-3-octadecanamido-2-ethyoxy-1-propylphosphocholine (hereinafter CP-51), rac-3-hexadecanamido-2-ethoxy-1-propylphosphocholine (hereinafter CP-49), 2-hexadecylthio-1-ethylphosphocholine (hereinafter CP-9), and rac-3-octadecyloxy-2-hydroxy-1-propyl phosphocholine (hereinafter lyso PAF).

Compounds of Formula II can be synthesized according to known procedures. See, e.g., Lipids 22 (11), 775-980 (1987); exemplary synthetic procedures are set forth below in the Examples. Among numerous noteworthy subsequent developments are the sulfur-containing phospholipids described in U.S. Patent No. 4,444,766 to Bosies et al., the phosphoric acid ester derivatives of 1,3-Dioxy propane disclosed in U.S. Patent No. 4,426,525 to Hozumi et al., the cyclammonium salts disclosed (as platelet activating factor inhibitors) in U.S. Patent No. 4,619,917 to Lee et al., and the lipoidal amine disclosed by J. Wolff et al., Cancer Immunol. Immunother. 12:97-98 (1982).

Another aspect of the invention is the inhibition of HBV-DNA and HBV antigen virion production using an alkyl ether phospholipid of Formula III, wherein R_1, Y, X, F, R_2, R_3, W and Z are defined as stated above, or a pharmaceutical salt thereof. Compounds of Formula III are amphipathic moieties having a hydrophobic end (R_1) linked to a hydrophilic alkyl ammonium-anion complex by a short alkyl backbone. wherein the polar, hydrophilic end is an inverse choline (e.g., N,N-dimethyl-β-hydroxyethyl ammonium).

R_1 can be an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl. As with the compounds of Formulas I and II, R_1 is a lipophilic moiety which binds with the cell membrane of infected cells to provide an anchor thereto. Preferably, R_1 is unbranched saturated or unsaturated C12-C20 alkyl. More preferably, R_1 is unbranched saturated or unsaturated C14-C18 alkyl.

As with the compounds of Formulas I and II, in compounds of Formula III Y is a functional group that links the lipophilic moiety R_1 and the short alkyl backbone of the compound. Y should be a functional group, such as S, O, NH, NCH_3, NHCO, or NCH_3CO, that is

able to withstand the hydrolytic activity of cellular lipases. Preferably, Y is S or NHCO.

The alkyl backbone of Formula III includes a constituent X which can be a covalent bond between the carbon atoms at either end of the backbone or a methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio. Preferably, X is a covalent bond or a methylene substituted with a hydroxyl or C1-C4 alkoxy; more preferably, X is methylene substituted with hydroxyl or methoxy.

The polar hydrophilic end of the amphipathic compounds of Formula III comprises an alkyl ammonium-anion complex wherein the anion, Z, carries the negative charge and the ammonium moiety carries the positive charge. In the alkyl ammonium moiety, F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl, W is OH or SH, and R_2 and R_3 are independently selected from the group consisting of hydrogen and C1-C3 alkyl. It is preferred that F is unsubstituted ethylene and W is OH. It is also preferred that R_2 and R_3 are each methyl. It is more preferred that F is unsubstituted ethylene, W is OH, and R_2 and R_3 are each methyl.

An exemplary compound of Formula III is N-[rac-3-(hexadecylthio)-2-methoxy-1-propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide (hereinafter CP-7).

In addition to CP-7 which is synthesized according to Example 5 below, compounds of Formula III can be synthesized by following the teachings of Example 5 in combination with procedures known to those skilled in the art.

An additional aspect of the invention is a method of inhibiting HBV-DNA and HBV antigen virion production using a compound of Formula IV, wherein R_1, Y, X, A, B and Base are defined as stated above, or a pharmaceutical salt thereof. Compounds of Formula IV are amphipathic moieties wherein the polar hydrophilic end is a phospho-nucleic acid conjugate.

In the compounds of Formula IV, the non-polar hydrophobic end is R_1, which can be an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl group. As for the compounds of Formulas I, II and III, R_1 is a lipophilic moiety which binds with the cell membrane of an HBV-infected cell to provide an anchor for the compound thereto. Preferably, R_1 is an unbranched saturated or unsaturated C12-C20 alkyl group. More preferably, R_1 is an unbranched saturated or unsaturated C14-C18 alkyl group.

As with the compounds of Formulas I, II and III, in compounds of Formula IV Y is a functional group that links the lipophilic moiety R_1 and the short alkyl backbone of the compound. Y should be a functional group, such as S, O, NH, NCH_3, NHCO, or NCH_3CO, that is able to withstand the hydrolytic activity of cellular lipases. Preferably, Y is S or NHCO.

The alkyl backbone of Formula IV includes a constituent X which can be a covalent bond between the carbon atoms at either end of the backbone or a methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio. Preferably, X is a covalent bond or a methylene substituted with a hydroxyl or C1-C4 alkoxy; more preferably, X is methylene substituted with hydroxyl or methoxy.

In the amphipathic compounds of Formula IV, the polar hydrophilic end of the compound comprises a phospho-nucleic acid conjugate. Many of the nucleic acid moieties that are suitable for use with the present invention are moieties that have shown anti-retroviral activity on other viruses by a different mechanism than that postulated herein, and thus are attached to the compounds of Formula IV to provide an additional impediment to viral activity. The nucleotide base is selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine. Thymine is a preferred base. A is hydrogen,

fluorine or N_3, and B is hydrogen or fluorine, or A and B together form a covalent bond (i.e., there is a double bond between A and B). It is preferred that A is hydrogen or N_3 and B is hydrogen. A particularly preferred nucleotide moiety is 3'-azido-3'deoxythymidine (AZT).

An exemplary compound of Formula IV is 3'-Azido-3'-deoxy-5'-(rac-3-dodecyloxy-2-decyloxy-1-propyl) phosphothymidine (hereinafter CP-126).

CP-126 and other compounds of Formula IV can be synthesized according to the method of PCT Application No. WO 91/19726 to Piantadosi et al., the entirety of which is herein incorporated by reference, and by the methods set forth in Example 4 below.

Experimentation has demonstrated the efficacy of the compounds of Formulas I, II, III, and IV in combatting HBV infection. For example, both compounds CP-49 and CP-51 substantially inhibited the levels of HBV virion DNA and intracellular RI HBV-DNA to levels comparable to, or greater than, that observed following evaluation of an internal positive control compound 2',3'-dideoxycytidine (ddC). Compounds CP-7, CP-9 and CP-126 were moderately inhibitory of HBV replication. The levels of virion DNA and RI HBV-DNA were reduced to amounts comparable to but slightly less than for ddC. In addition, CP-51 has been demonstrated to inhibit the production of the HBV antigens core antigen and e antigen. This result suggests that the mechanism of action of the compounds involves suppression of nucleocapsid and HBV pregenomic RNA packaging to form new HBV particles.

In the manufacture of a medicament according to the invention, hereinafter referred to as a "formulation," the compounds of Formulas I, II, III and IV are typically admixed with, among other things, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any

other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

The formulations of the invention include those suitable for oral, rectal, topical, intrathecal, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above).

Suitable solid diluents or carriers for the solid oral pharmaceutical dosage unit forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like.

Capsules, both hard and soft, are filled with compositions of these amino-amide active ingredients in

combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and the like, and also calcium stearate.

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, methylcellulose, acacia, polyvinylpyrrolidone, polyvinyl alcohol and the like.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, intrathecal, or intradermal

injection. The formulation should be sufficiently fluid that easy syringe ability exists. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Such preparations should be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the basic solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistatic agents, for example, parabens, chlorobutanol, benzyl alcohol, phenol, thimerosal, and the like. In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Injectable formulations according to the invention generally contain from 0.1 to 5% w/v of active compound and are administered at a rate of 0.1 ml/min/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w, for example, from 0.5 to 2% w/w.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1

to 0.2M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, Pharmaceutical Research 3 (6), 318, (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The compounds of Formulas I, II, III and IV are administered in an amount sufficient to inhibit HBV-DNA and virion production. The dose can vary depending on the compound selected for administration, the subject, the route of administration, and other factors. Preferably, the compound is administered in an amount of at least 0.1 ng/kg, 1 ng/kg, 0.001 μg/kg or more, and is adminstered in an amount no greater than 0.1 g/kg, 0.01 g/kg, 1 mg/kg, or less.

The invention is illustrated in greater detail in the following non-limiting examples. In the Examples, "μg" means micrograms, "pg" means picograms, "nM" means nanomolar, "μM" means micromolar, "ml" means milliliters, "°C" means degrees Celsius, "DMF" means dimethylformamide, "mol" means moles, "mmol" means millimoles, and "Kb" means Kilobases.

EXAMPLE 1

Preparation of (±)-3-N-Octadecanamido-2-ethoxypropyl-1-phosphocholine

A. Preparation of (+)-3-Octadecanamido-1,2-propanediol

To a mechanically stirred solution of 3-amino-1,2-propanediol (32 g, 0.35 mol) in 100 mL of pyridine and 250 mL of DMF was added a solution of stearoyl chloride (100.0 g, 0.33 mol) in 150 mL of DMF. After stirring for 1 h, precipitation occurred and an

additional 100 mL of DMF was added. After 2 h, the gelatinous mass was filtered, washed with water, and air dried. The solid was recrystallized successively from EtOH, isopropanol, and chloroform to give 74 g (63%) as a white powder (mp 111.5-113.5°C). ^{1}H-NMR: 0.86 (t, 3H, CH_3), 1.25 (broad m, 28H, $(CH_2)_{14}$), 1.55 (m, 2H, $NHCOCH_2\underline{CH_2}$), 2.20 (t, 2H $NHCO\underline{CH_2}$), 3.4 (m, 2H, $\underline{CH_2}NH$), 3.55 (d, 2H, $\underline{CH_2}OH$). 3.75 (m, 1H, CH), 5.8 (m, 1H, NH)..

B. Preparation of (+)-3-N-Octadecanamido-1-triphenylmethory-2-propanol

Trityl chloride (40 g, 0.11 mol) was added to a stirring solution of (+)-3-octadecanamido-1,2-propanediol (35 g, 0.1 mol) in 250 mL of pyridine. The reaction mixture was heated to 45-50°C for 10 h. After removing the pyridine under reduced pressure, the residue was diluted with 100 mL of water and extracted three times with 100 mL of chloroform. The combined extracts were washed with 50 mL each of cold, 5% HCl and saturated NaCl, dried over sodium sulfate, filtered, and evaporated to dryness. The crude residue was recrystallized two times from hexane, thereby giving 43 g (72%, mp 86-88°C) of the trityl ether. ^{1}H-NMR: 0.90 (t, 3H, CH_3), 1.25 (broad m, 28H, $(CH_2)_{14}$), 1.55 (m, 2H, $NHCOCH_2\underline{CH_2}$), 2.10 (t, 2H, $NHCO\underline{CH_2}$), 3.15 (overlapping m, 3H, $\underline{CH_2}NH$, $CH\underline{H}'OTr$), 3.5 (m, 1H, $CH\underline{H}'OTr$), 3.85 (m, 1H, CH), 5.6 (m, 1H, NH), 7.35 (m, 15H, aromatic H).

C. Preparation of (+)-3-N-Octadecanamido-2-ethoxy-1-triphenylmethoxypropane

A solution of (+)-3-N-Octadecanamido-1-triphenylmethory-2-propanol (28 g, 0.045 mol) in 100 mL THF was added to a slurry of 80% NaH (1.8 g, 0.05 mol) in 10 mL THF. After stirring for 30 min at room temperature, ethyl iodide (4 mL, 7.8 g, 0.05 mol) was added and the reaction mixture heated to 50°C for 2 h. An additional 0.3 g NaH and 2 mL of EtI was added and heating continued for 2 h. After cooling, water was

added slowly to decompose any residual NaH. Diethyl ether (100 mL) was added and the layers separated. The aqueous layer was reextracted with ether and the organic extracts combined, washed with brine, and dried over sodium sulfate. The crude product was dissolved in hot hexane and a small amount of insoluble material filtered and discarded. After cooling at 0°C, 21.7 g (78%, mp 58-61°C) of product was obtained. Chromatography of silica gel using hexane: ^{1}H-NMR: 0.80 (t, 3H, CH_3), 1.25 (broad m, 31H, $(CH_2)_{14}$, $OCH_2\underline{CH_3}$), 1.55 (m, 2H, $NHCOCH_2\underline{CH_2}$), 2.15 (t, 2H, $NHCO\underline{CH_2}$), 3.1.-3.7 (m, 7H, $\underline{CH_2}N$, $\underline{CHCH_2}OH$, $\underline{OCH_2}CH_3$), 5.7 (m, 1H, NH), 7.25 (m, 15H, aromatic H).

D. Preparation of (+)-3-N-Octadecanamido-2-ethoxy-1-propanol

p-Toluenesulfonic acid (1 g, 0.005 mol) was added to a solution of (+)-3-N-Octadecanamido-2-ethoxy-1-triphenylmethoxypropane (21.7 g, 0.035 mol) in 100 mL of methylene chloride and 20 mL of methanol. The solution was stirred for 8 h at room temperature. Saturated sodium bicarbonate was added and stirred for 0.5 h. The layers were separated and the organic fraction washed with brine. After drying over sodium sulfate, the solution was concentrated in vacuo. Crude product was obtained by precipitation from hexane. Chromatography on silica gel with a gradient of methylene chloride: methanol (100:0 to 95:5) gave 9 g (69%, mp 79-80°C) as a white solid. ^{1}H-NMR: 0.85 (t, 3H, CH_3), 1.25 (broad m, 31H, $(CH_2)_{14}$, $OCH_2\underline{CH_3}$), 1.55 (m, 2H, $NHCOCH_2\underline{CH_2}$), 2.20 (t, 2H, $NHCO\underline{CH_2}$), 3.3-3.9 (overlapping m, 7H, $\underline{CH_2}N$, $\underline{CHCH_2}OH$, $\underline{OCH_2}CH_3$), 5.9 (m, 1H, NH).

E. Preparation of (+)-3-N-Octadecanamido-2-ethoxypropyl-1-phosphocholine (CP-51)

To a cooled (ice bath) stirring solution of (+)-3-N-Octadecanamido-2-ethoxy-1-propanol (1.0 g, 0.0026 mol) and triethylamine (0.29 g, 0.0029 mol) in 40 mL of dry benzene was added 2-chloro-2-oxo-1,3,2-

dioxophospholane (0.41 g, 0.0029 mol) in 4 mL benzene. The reaction mixture was stirred at room temperature for 4 h. The precipitate was filtered and washed with benzene. The filtrate was concentrated and the intermediate phosphotriester was used without further purification. The solid was transferred to a dry pressure flask containing 40 mL of dry acetonitrile and cooled in a dry ice/acetone bath. Trimethylamine (3 mL) was condensed and added to the reaction vessel. The flask was sealed and the reaction mixture heated to 65°C overnight. A white solid formed upon cooling and was filtered and precipitated from chloroform: acetone (1:10). Chromatography on silica gel eluting with chloroform: methanol: ammonium hydroxide (70:35:2 to 70:35:5) gave pure product (0.6 g, 42%, hygroscopic solid, decomposes 245°C) which was precipitated again from chloroform: acetone. ^{1}H-NMR: 0.85 (t, 3H, CH_3), 1.15 (t, 3H, $OCH_2\underline{CH_3}$), 1.25 (broad m, 28H, $(CH_2)_{14}$), 1.60 (m, 2H, $NHCOCH_2\underline{CH_2}$), 2.18 (t, 2H, $NHCO\underline{CH_2}$), 3.35 (s, 9H, $N(CH_3)_3$), 3.3-3.7 (overlapping m, 6H, $\underline{CH_2}N(CH_3)_3$, $\underline{CH_2}NH$, $\underline{OCH_2}CH_3$), 3.7-4.1 (m, 3H, CH, CH_2OP), 4.35 (m, 2H, $POCH_2$), 7.1 (m, 1H, NH).

Elemental analysis $C_{28}H_{59}N_2O_6P'H_2O$

EXAMPLE 2

Preparation of (±)-3-N-Hexadecanamido-2-ethoxypropyl-1-phosphocholine (CP-49)

This compound was prepared by the same procedure set forth in Examples 1 with the substitution of palmitoyl chloride for stearoyl chloride in the reaction described in section A. above.

EXAMPLE 3

Preparation of 2-(Hexadecylthio)ethyl phosphocholine (CP-7)

A. Preparation of 2-(Hexadecylthio)ethanol

Thioethanol (5.0 g, 64 mmol), hexadecyl bromide (25.0 g, 82 mmol), and KOH (4.5 g, 80 mmol) were combined

in 95% EtOH (150 mL). The reaction mixture was stirred at room temperature overnight and then diluted with H_2O. The precipitate was collected and recrystallized from MeOH to provide the thioether: 19.0 g, 96%; mp 50°C; NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3 H, CH_3), 1,30 (m, 26 H, $(CH_2)_{13}$), 1.60 (m, 2 H, CH_2CH_2S), 2.52 (t, 2 H, SCH_2), 2.72 (m, 2 H, CH_2S), 3.72 (m, 2 H, CH_2OH).

B. Preparation of 2-(Hexadecylthio) ethylphosphocholine (CP-9)

2-(Hexadecylthio)ethanol (1.0 g, 3.0 mmol) and Et_3N (0.40 g, 4.0 mmol) were dissolved in anhydrous benzene (75 mL). The solution was cooled to 0°C before a solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (0.65 g, 4.6 mmol, Fluka) in anhydrous benzene was slowly added. The reaction mixture was stirred overnight at room temperature and then filtered. The filtrate was reduced, and the residue was dissolved in CH_3CN (50 ml) and transferred to a glass bomb. Condensed $N(CH_3)_3$ (2.0 g, 34 mmol) was added, and the mixture was heated at a gentle reflux for 24 h. Upon cooling of the reaction mixture, a white precipitate formed. The solid was removed and recrystallized with Et_2O to provide 980 mg of **2-(Hexadecylthio)ethylphosphocholine**. 70%; dec > 200°C; NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3 H, CH_3), 1.21 (s, 26 H, $(CH_2)_{13}$), 1.53 (m, 2 H, CH_2CH_2S), 2.51 (t, 2 H, SCH_2), 2.72 (t, 2 H, CH_2S), 3.37 (s, 9 H, $N(CH_3)_3$), 3.81 (m, 2 H, CH_2N), 3.91 (m, 2 H, CH_2OP), 4.31 (m, 2 H, $POCH_2$); FAB MS *m/e* 468 (MH+).

EXAMPLE 4

Preparation of 3'-Azido-3'-deoxy-5'-(3-dodecyloxy-2-decyloxypropyl)-phosphothymidine (CP-126)

A. Preparation of 3-Dodecyloxy-1,2-propanediol

Isopropylideneglycerol (solketal, 26.4 g, 0.20 mol) in 60 mL of toluene was added dropwise to a solution of powered KOH (22.4 g, 0.04 mol) in 150 mL of toluene. The resulting mixture was refluxed for 4 h. 1-

bromododecane (50 g, 0.20 mol) in 40 mL of toluene was then added dropwise, and the solution was refluxed for 10 h. After cooling, the reaction mixture was diluted with 200 mL of ice-water and extracted with diethyl ether (3 X 100 mL). The ether layers were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in 60 mL of diethyl ether and 260 mL of MeOH. Concentrated HCl (60 mL) was added, and the solution refluxed for 16 h. After cooling, ice-water (150 mL) was added, and the layers separated. The aqueous layer was extracted with diethyl ether (2 X 75 mL). The combined organic fractions were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The solid residue was recrystallized from MeOH to give 37 g (0.14 mol, 71%) of a white solid.

B. Preparation of 3-Dodecyloxy-1-triphenylmethoxy-2-propanol

The diol produced in section A was tritylated with trityl chloride (59 g, 0.21 mol) in pyridine (200 mL) at 70°C for 5 h and then at room temperature overnight. The pyridine was removed under vacuum, and the solid residue partitioned between water and $CHCl_3$. The $CHCl_3$ layer was washed with 5% HCl and water, then dried over magnesium sulfate. After removal of solvent, the product was recrystallized from hexanes:ethyl acetate (10:1) to give 19 g of pure 3-Dodecyloxy-1-triphenylmethoxy-2-propanol.

C. Preparation of 3-Dodecyloxy-2-decyloxy-1-triphenylmethoxypropane

3-Dodecyloxy-1-triphenylmethoxy-2-propanol (13.5 g, 0.027 mol) was added dropwise to an ice-cooled suspension of sodium hydride (80%, 1.6 g, 0.054 mol) in 150 mL of tetrahydrofuran under nitrogen. After stirring for 2 h at room temperature, heat was applied (55°C). 1-Bromodecane (6 g, 0.027 mol) was added dropwise, and heating continued for 6 h. After cooling for 3 h, water

was added slowly. Diethyl ether (2 X 100 mL) was added, and the solution washed with 15% sodium thiosulfite, water, and brine. After drying over sodium sulfate, the ether was removed, and the residue chromatographed with a gradient of hexanes:ethyl acetate (100:0 to 20:1) to give 9 g (52%) of a clear liquid.

D. Preparation of 3-Dodecyloxy-2-decyloxy-1-propanol

Detritylation of 3-Dodecyloxy-2-decyloxy-1-triphenylmethoxypropane was accomplished using p-toluenesulfonic acid (0.9 g) in $CHCl_3$:MeOH (72 mL:36 mL) (stirred at room temperature for 48 h, added 10% sodium bicarbonate, extracted with $CHCl_3$, dried over magnesium sulfate, and concentrated). The residue was purified by column chromatography using a gradient of hexanes:ethyl acetate (20:1 to 5:1) to give 3.5 g (63%) of pure 3-dodecyloxy-2-decyloxy-1-propanol.

E. Preparation of 3-Dodecyloxy-2-decyloxypropyl Diphenyl Phosphate

Diphenylchlorophosphate (0.7 mL, 3.4 mmol) in 10 mL of diethyl ether was cooled to 4°C under nitrogen. 3-Dodecyloxy-2-decyloxy-1-propanol (1.0 g, 2.6 mmol) in 15 mL of pyridine and 5 mL of diethyl ether was added. The solution was warmed to room temperature, then heated to 52°C for 3 h. It was then cooled to room temperature, diluted with 50 mL of diethyl ether, washed with water (2 X 25 mL), 0.5 N HCl (25 mL), and finally with water (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to an oil. Chromatography with a gradient of hexanes:ethyl acetate (10:1 to 1:1) gave 980 mg (1.5 mmol, 60%) of pure product.

F. Preparation of 3-Dodecyloxy-2-decyloxypropyl Phosphate

PtO_2 (69 mg) was placed in a Parr hydrogenation bottle. 3-Dodecyloxy-2-decyloxypropyl Diphenyl Phosphate (500 mg) in 100 mL of EtOH was then added. The reaction mixture was hydrogenated at 15 psi for 1.5 h until hydrogen uptake stopped. The reaction mixture was then filtered through Celite, and the EtOH removed *in vacuo*. The oil residue was dissolved in 25 mL of pyridine, concentrated *in vacuo*, and dried under high vacuum to give 350 mg of pure solid phosphatidic acid.

G. Preparation of 3'-Azido-3'-deoxy-5'-(3-dodecyloxy-2-decyloxypropyl)-phosphothymidine (CP-126)

AZT (43 mg, 0.16 mmol) and 3-Dodecyloxy-2-decyloxypropyl phosphate (105 mg, 0.22 mmol) were azeotrophically dried with pyridine (3 X 3 mL) by *in vacuo* removal. Dicyclohexylcarbodiimide (220 mg, 1.07 mmol) was added and the drying repeated 4 times. A final 3 mL portion of pyridine was added, and the reaction mixture stirred at room temperature in a desiccator for 4 days. Water (1 g) was added, and the mixture stirred for 4 h. The solvents were removed in vacuo, and the crude material chromatographed on 2 g of silica gel using a gradient of $CHCl_3$:MeOH (15:1 to 2:1). The product was dissolved in 11 mL of $CHCl_3$:MeOH:H_2O (4:6:1) and stirred with 1.5 g of Whatman preswollen microgranular cation (Na+) exchange (carboxymethyl)-cellulose resin for 1 h to obtain the sodium salt. The resin was filtered and concentrated *in vacuo* to give 37 mg of 3'-Azido-3'-deoxy-5'-(3-dodecyloxy-2-decyloxypropyl)-phosphothymidine (CP-126) (22%). FAB ms showed a [MH+Na]+ ion at 752.4350 ($C_{35}H_{64}N_5O_9PNa$, 1.4 ppm) and a [M+2Na]+ ion at 774.4179 ($C_{35}H_{63}N_5O_9PNa_2$, 2.0 ppm).

EXAMPLE 5

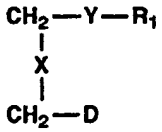
Synthesis of N-[rac-3-(hexadecylthio-2-methoxy-1-propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide (CP-7)

Into a two neck 25 ml round bottom flask equipped with an air condenser, thermometer and stir bar, was placed 2.0 g (0.005 mol) of (±)-1-hexadecylthio-2-0-methoxy-3-bromopropane, 0.5 ml (0.006 mol) of N,N-dimethylaminoethanol and 15 ml of DMF. The solution was maintained at 45-50°C for 72 hours with continuous stirring. The reaction mixture was then cooled to room temperature, 125 ml of ether was added and the solution was kept at 0°C for 24 hours. The resulting precipitate (800 mg) was filtered and swirled with five 50 ml portions of ether to give (±)-3-hexadecylthio-2-methoxy-N,N-dimethyl-N-ß-hydroxyethyl-1-propyl ammonium bromide (32%), (mp 107-109°C). ^{1}H-NMR ($CDCl_3$): delta, 0.87 (t, 3 H, terminal methyl), 1.2-1.6[m, 28 H, $(CH_2)_{14}$], 2.45-3.0(m, 4 H, S-CH_2, CH_2-S), 3.48[s, 9 H, CH_3-O, N$(CH_3)_2$], 3.9-4.3(m, 7 H, CH, CH_2N, N-CH_2-CH_2-OH). Anal. ($C_{24}H_{52}NO_2SBr$) C,H,N.

The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

CLAIMS:

1. A method of combatting infection with hepatitis B virus comprising administering to a subject in need of such treatment an effective hepatitis B-combatting amount of a compound of Formula I:



(I)

wherein

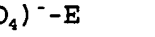
Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl;

X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

and D is selected from the group consisting of moieties of Formula V or Formula VI;

wherein Formula V is

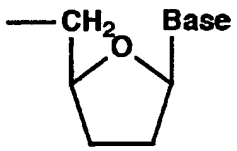


(V)

wherein E is selected from the group consisting of:

$-F-N^+(R_2)(R_3)(R_4)$, wherein F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl; and R_2, R_3, and R_4 are independently selected from the group consisting of H and C1-C3 alkyl; and

a nucleic acid base conjugate of the Formula VII



(VII)

wherein the base is selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine; A is H, F, or N_3; and B is H or F, or A and B together form a covalent bond;

and wherein Formula VI is

$$-N^{+}(R_5)(R_6)-F-W\ Z^{-} \qquad \text{(VI)}$$

wherein R_5 and R_6 are independently selected from the group consisting of H and C1-C3 alkyl;

F is as defined above;

W is -OH, or -SH; and

Z^{-} is an anion;

or a pharmaceutical salt thereof.

2. A method according to claim 1, wherein Y is NHCO.

3. A method according to claim 1, wherein R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

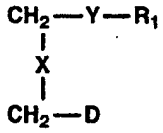
4. A method according to claim 1, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

5. A method according to claim 1, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

6. A method according to claim 1, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

7. A method according to claim 1, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

8. A method of inhibiting the production of hepatitis B virus antigens selected from the group consisting of core and e antigens in a subject, said method comprising administering an antigen inhibiting amount of a compound of Formula I:



(I)

wherein

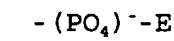
Y is S, O, NH, NCH_3, NHCO, or NCH_3CO;

R_1 is unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl;

X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio;

and D is selected from the group consisting of moieties of Formula V or Formula VI;

wherein Formula V is

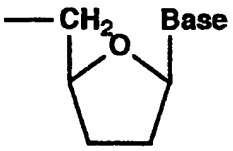


(V)

wherein E is selected from the group consisting of:

$-F-N^{+}(R_2)(R_3)(R_4)$, wherein F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl; and R_2, R_3, and R_4 are independently selected from the group consisting of H and C1-C3 alkyl; and

a nucleic acid base conjugate of the Formula VII



(VII)

wherein the base is selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine; A is H, F, or N_3; and B is H or F, or A and B together form a covalent bond;

and wherein Formula VI is

$$-N^{+}(R_5)(R_6)-F-W\ Z^{-} \qquad \text{(VI)}$$

wherein R_5 and R_6 are independently selected from the group consisting of H and C1-C3 alkyl;

F is as defined above;

W is -OH, or -SH; and

Z^{-} is an anion;

or a pharmaceutical salt thereof.

9. A method according to claim 8, wherein Y is NHCO.

10. A method according to claim 8, wherein R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

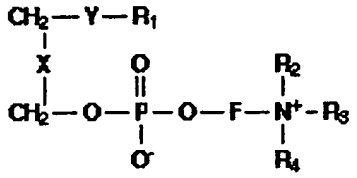
11. A method according to claim 8, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

12. A method according to claim 8, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

13. A method according to claim 8, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

14. A method according to claim 8, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

15. A method of combatting infection with hepatitis B virus comprising administering a subject in need of such treatment an effective hepatitis B-combatting amount of a compound of Formula II:



(II)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl; X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio; F is C1-C4 alkyl optionally substituted one to three times with methyl or ethyl; and R_2, R_3, and R_4 are independently selected from the group consisting of H and C1-C3 alkyl; or a pharmaceutical salt thereof.

16. A method according to claim 15, wherein F is ethylene, and wherein R_2, R_3, and R_4 are each methyl.

17. A method according to claim 15, wherein Y is NHCO.

18. A method according to claim 15, wherein R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

19. A method according to claim 15, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

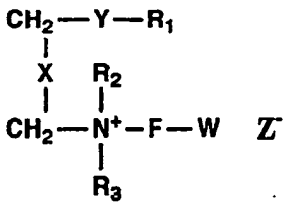
20. A method according to claim 16, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

21. A method according to claim 16, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

22. A method according to claim 16, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

23. A method according to claim 15, wherein the hepatitis B combatting compound of Formula II is selected from the group consisting of rac-3-octadecanamido-2-ethyoxy-1-propylphosphocholine, rac-3-hexadecanamido-2-ethoxy-1-propylphosphocholine, 2-hexadecylthio-1-ethylphosphocholine, and rac-3-octadecyloxy-2-hydroxy-1-propyl phosphocholine.

24. A method of combatting infection with hepatitis B virus comprising administering a subject in need of such treatment an effective hepatitis B-combatting amount of a compound of Formula III:



(III)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl, X is a covalent bond or methylene optionally substituted 1 or 2 times with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio, F is C_1-C_4 alkyl optionally substituted 1 to 3 times with methyl or ethyl, R_2 and R_3 are independently selected from the group consisting of H and C1-C3 alkyl, and W is -OH, or -SH.

25. A method according to claim 24, wherein f is ethylene, and wherein R_2 and R_3 are each methyl.

26. A method according to claim 24, wherein Y is S and R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

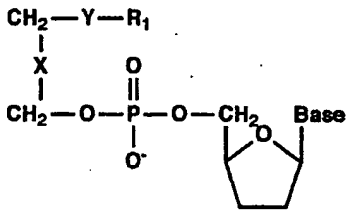
27. A method according to claim 24, wherein X is methylene substituted with methoxy or ethoxy.

28. A method according to claim 24, wherein Z^- is halogen.

29. A method according to claim 25, wherein R_1 is C14-C18 unbranched saturated or unsaturated alkyl, Y is S or NHCO, X is methylene substituted with methoxy or ethoxy, and W is -OH.

30. A method according to claim 24 wherein the hepatitis B combatting compound of formula III is N-[rac-3-(hexadecylthio)-2-methoxy-1-propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide.

31. A method of combatting infection with hepatitis B virus comprising administering a subject in need of such treatment an effective hepatitis B-combatting amount of a compound of Formula IV:



(IV)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl, X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio; Base is a base selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine; A is H, fluorine, or N_3; and B is H or fluorine or A and B together form a covalent bond.

32. A method according to claim 31, wherein A is H or N_3 and B is H.

33. A method according to claim 31, wherein Y is NHCO.

34. A method according to claim 31, wherein R_1 is an unbranched saturated or unsaturated C14-C18 alkyl.

35. A method according to claim 31, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

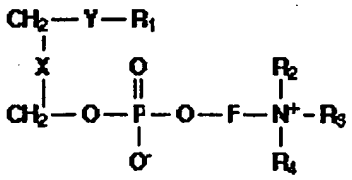
36. A method according to claim 32, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

37. A method according to claim 32, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

38. A method according to claim 32, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

39. A method according to claim 31, wherein the hepatitis B combatting compound is 3'-Azido-3'-deoxy-5'-(rac-3-dodecyloxy-2-decyloxy-1-propyl) phosphothymidine.

40. A method of inhibiting the production of hepatitis B virus antigens selected from the group consisting of core and e antigens in a subject, said method comprising administering an antigen inhibiting amount of a compound of Formula II:



(II)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl; X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio; F is C_1-C_4 alkyl optionally substituted 1 to 3 times with methyl or

ethyl, and R_2, R_3 and R_4 are independently selected from the group consisting of H and C1-C3 alkyl, or a pharmaceutical salt thereof.

41. A method according to claim 40, wherein F is unsubstituted ethylene, and wherein R_2, R_3, and R_4 are each methyl.

42. A method according to claim 40, wherein Y is NHCO.

43. A method according to claim 40, wherein R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

44. A method according to claim 40, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

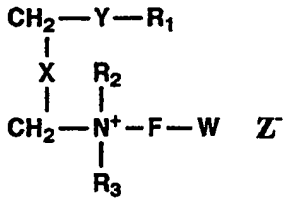
45. A method according to claim 41, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

46. A method according to claim 41, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

47. A method according to claim 41, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

48. A method according to claim 41, wherein the hepatitis B antigen inhibiting compound of Formula II is selected from the group consisting of rac-3-octadecanamido-2-ethyoxy-1-propylphosphocholine, rac-3-hexadecanamido-2-ethoxy-1-propylphosphocholine, 2-hexadecylthio-1-ethylphosphocholine, rac-3-octadecyloxy-2-hydroxy-1-propyl phosphocholine.

49. A method of inhibiting the production of hepatitis B virus antigens selected from the group consisting of core and e antigens in a subject, said method comprising administering an antigen inhibiting amount of a compound of Formula III:



(III)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl; X is a covalent bond or methylene optionally substituted 1 or 2 times with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio; F is C_1-C_4 alkyl optionally substituted 1 to 3 times with methyl or ethyl; R_2 and R_3 are independently selected from the group consisting of H and C1-C3 alkyl; and W is -OH, or -SH.

50. A method according to claim 49, F is ethylene, and wherein R_2, and R3 are each methyl.

51. A method according to claim 49, wherein Y is S and R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

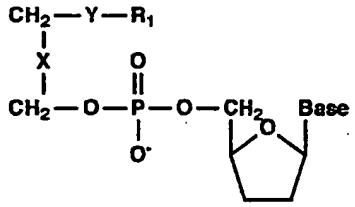
52. A method according to claim 49, wherein X is methylene substituted with methoxy or ethoxy.

53. A method according to claim 49, wherein Z^- is halogen.

54. A method according to claim 50, wherein R_1 is C14-C18 unbranched saturated or unsaturated alkyl, Y is S, X is methylene substituted with methoxy or ethoxy, and W is -OH.

55. A method according to claim 49 wherein the hepatitis B antigen inhibiting compound of formula III is N-[rac-3-(hexadecylthio)-2-methoxy-1-propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide.

56. A method of inhibiting the production of hepatitis B virus antigens selected from the group consisting of core and e antigens in a subject, said method comprising administering an antigen inhibiting amount of a compound of Formula IV:



(IV)

wherein Y is S, O, NH, NCH_3, NHCO, or NCH_3CO; R_1 is an unbranched or branched, saturated or unsaturated C10-C20 alkyl, alkenyl, or alkynyl; X is a covalent bond or methylene optionally substituted with hydroxyl, C1-C10 alkyl, C1-C10 alkoxy, or C1-C10 alkylthio; Base is a base selected from the group consisting of thymine, adenine, cytosine, guanine, hypoxanthine, uracil, and 2-amino adenine; A is H, fluorine, or N_3; and B is H or fluorine or A and B together form a covalent bond.

57. A method according to claim 56, wherein A is H or N_3 and B is H.

58. A method according to claim 56, wherein Y is NHCO.

59. A method according to claim 56, wherein R_1 is unbranched saturated or unsaturated C12-C20 alkyl.

60. A method according to claim 56, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy.

61. A method according to claim 57, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is NHCO, and R_1 is C14-C18 alkyl.

62. A method according to claim 57, wherein X is methylene substituted with hydroxyl or C1-C4 alkoxy, Y is S, and R_1 is C14-C18 alkyl.

63. A method according to claim 57, wherein X is a covalent bond, Y is S, and R_1 is C14-C18 alkyl.

64. A method according to claim 56, wherein the hepatitis B antigen inhibiting compound is 3'-Azido-3'-deoxy-5'-(rac-3-dodecyloxy-2-decyloxy-1-propyl) phosphothymidine.